CASE N-32809A

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
GIBSON ET AL.
APPLICATION NO: Not Yet Assigned
FILED:
FOR: PREBIOTIC COMPOSITIONS

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

CLAIM OF PRIORITY UNDER 35 USC §119

Sir:

Applicants in the above-identified application hereby claim priority under the International Convention of Great Britain Application No. 0229015.3, filed on December 12, 2002 This application is acknowledged in the Declaration of the instant case.

The certified copy of said application is submitted herewith.

Respectfully submitted,

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Date: November 25, 2003

N- 32809 P1

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3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS NUTRITION AG MONBIJOUSTRASSE 118 3001 BERN SWITZERLAND
	Patent ADP number *(if you know it)*	7143563001
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	New compound
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New Compound

The present invention concerns compositions comprising soluble fibers, in particular FOS, and their use in the treatment or prevention of gastrointestinal tract disorders, such as IBS or IBD.

Prebiotics are non-digestible food ingredients which have a beneficial effect on the health. For a food ingredient to be classified as a prebiotic it must fulfill the following criteria: i) neither be hydrolyzed, nor absorbed in the gastrointestinal tract, ii) be selectively fermented by one or a limited number of potentially beneficial bacteria commensal to the colon, such as lactobacilli and bifidobacteria, which are stimulated to grow and/or become metabolically activated, iii) be able to alter the colonic microflora towards a healthier composition, by increasing, for example, numbers of saccharolytic species while reducing putrefactive microorganisms. Bifidobacteria are obligate anaerobes that metabolize carbohydrates to acetic and lactic acids, which are further metabolized by host tissues. They are thought to play an important role in the protection from enteric infection, the suppression of putrefactive and pathogenic bacteria, the production of vitamins, the activation of intestinal function, the assistance of digestion and absorption, as well as the stimulation of the immune response. Because Bifidobacteria are susceptible to oxygen and heat, their application in foods has been limited. Therefore, there has been an increased interest in prebiotics, which show effectiveness and endure normal food processing.

A desirable attribute for prebiotics is the ability to persist towards distal region of the colon. This region of the gut is the site of origin of several chronic disease states including colon cancer and ulcerative colitis. It is thought that the microflora in this region of the gut may play an important role in the onset or maintenance of such disorders. Dietary carbohydrate is the main fermentable substrate in the proximal colon and as this is degraded during bacterial fermentation, protein takes over as the dominant fermentable substrate towards more distal regions. The products of bacterial protein metabolism include toxic and potentially carcinogenic compounds such as amines, ammonia and phenolic compounds.

Inflammatory bowel disease (IBD) is a group of disorders that cause inflammation or ulceration in the small and large intestines. Most often, IBD is classified either as ulcerative colitis or Crohn's disease.

IDB may predispose to colon cancer. Aetiology is unknown, and cannot be cured by current drug therapy. Many factors are implicated, in particular genetic, environmental, immune and microbial.

Ulcerative colitis, also called colitis, ileitis or proctitis, is an inflammatory reaction usually occurring in the rectum and lower part of the colon, or may affect the entire colon. This pathogenesis causes heamorrhage, bloody diarrhea, rectal bleeding pain, fever, weight loss, and can also induce complications such as colon perforation, conjunctivitis, abscesses, mouth ulcers, skin lesions. Several studies implicate sulphate-reducing bacteria, such as *Desulfovibrio,* in Ulcerative Colitis pathogenesis. These bacteria, which reduce sulphate to sulphide, are present in 50% of healthy population but ubiquitous in people suffering from ulcerative colitis (97 to 100%); they increase sulfidogenesis in IBD patients, and induce damages such as impairing butyrate oxidation, compromising epithelia cell barrier, inducing translocation of bacteria and food antigens and inflammation. Other bacteria may be involved in UC, such as E.coli. Paratuberculosis, Holiobacter spp. Ulcerative colitis cannot be cured by current drug therapy but it is managed through the use of anti-inflammatory pharmaceuticals. The drugs which can be used to treat patients with mild or moderate disease, such as sulfasalazine, may induce side effects, like nausea, vomiting, diarrhea or headache. Corticosteroids may be used in more severely sick patients, but may in particular increase risk of infection. In severe cases, surgery is needed to remove the diseased colon.

Crohn's disease differs from ulcerative colitis because it causes inflammation deeper within the intestinal wall. Crohn's disease usually occurs in the small intestine. It is a chronic condition and may occur at various times over a lifetime

Irritable bowel syndrome (IBS) is characterized by a combination of persistent and recurrent abdominal pain and abdominal bowel habits such as diarrhea, constipation or both. IBS cannot be cured by current drug therapy.

In recent years, there is on the part of the consumers an increasing demand of foodstuffs that in addition to having a nutritional value also have a positive impact on health. In

particular there is an interest in developing functional foods containing prebiotics with extended fermentation times capable of reaching the distal bowel and increasing numbers of bifidobacteria. *In vivo* human studies have shown that dietary addition of FOS leads to an increase in faecal bifidobacteria and is a very effective prebiotic. Nevertheless, high levels of FOS may lead to excessive gas production in human volunteers and the lowest efficacious amount of FOS should be used in the production of prebiotic foods. Therefore there is a need for developing new prebiotic compositions.

Present inventors have surprisingly found that the prebiotic properties of FOS and GOS are more than additive, i.e. a synergistic effect in promoting the growth of Bifidobacteria and Lactobacilli was observed.

As a result of this synergy, it is possible to obtain an equivalent or improved prebiotic effect of FOS at lower dosages compared with conventional prebiotic products. This has the advantage that a powerful prebiotic effect can be achieved *in vivo* while avoiding the need to ingest any single prebiotic at levels that could threaten health. In addition, the maximum prebiotic benefit obtainable is superior to the maximum benefit obtainable through use of these prebiotic separately.

The intake of dietary fibers, particularly of fructans and/or resistant oligosaccharides, increases the density of lactic acid producing bacteria in the gastro-intestinal tract and reduces the number of undesirable Enterobacteriaceae. The latter include most pathogens such as e. g. bacteria of the genus Clostridia, Bacteroides, Listeria, Candida and Salmonella. Accordingly, intake of dietary fibers such as fructans and/or oligofructose can be used to selectively stimulate the growth of beneficial bacteria in the gastro-intestinal tract. The improvement of the ratio beneficial/pathogenic bacteria in turn results in beneficial health effects for the host.

As used herein, the term "oligosaccharide" refers to saccharide consisting of at least two, up to 20 glycosidically linked monosaccharide units, i.e. having a degree of polymerization (DP) of 2 to 20, preferably of 2 to 15 monosaccharide units, more preferably of 2 to 10 monosaccharide units, and even more preferably of 2 to 7 monosaccharide units.

Examples of suitable oligosaccharides according to the present invention include FOS, GOS, lactulose, XOS, SOS, IMO, ABG, soybean-oligosaccharide, gentio-oligosaccharide, fructans, short chain FOS and mixtures thereof, preferably FOS, GOS, XOS, short chain FOS, PHGG and mixtures thereof, and even more preferably FOS, GOS, PHGG and mixtures thereof

Fructo-oligosaccharides (also called oligofructose) (FOS) are indigestible oligosaccharides that are members of the inulin subclass of fructans. FOS occur in nature in many kind of plants, including onions, garlic, shallots, wheat, rye, bananas, aspergus, tomatoes, artichokes, dahlia and chicory root. FOS can be produced enzymatically, through chemical techniques or by extraction from natural substances. Short chain FOS are composed of one to three fructose molecules linked to one molecule of sucrose: their polymerization degree (DP) is not higher than 6, and they can be synthesized from sucrose through the use of transfructosylating enzymes. Treatment of sucrose with these transfructosylating enzymes results in a mixture of FOS containing 2, 3 or 4 fructose units, such as 1-kestose, nystose and fructosyl-nystose. *In vivo* human studies have been shown that dietary addition of FOS leads to an increase in faecal bifidobacteria and is a very effective prebiotic.

As used herein the term "FOS" encompass FOS and short chain FOS. According to the invention, FOS may comprise between 2 and 20 saccharide units, preferably between 2 to 15 saccharide units, more preferably between 2 to 7 saccharide units and even more preferably between 2 to 6 saccharide units. In one embodiment of the invention, FOS may contain about 95% by weight disaccharides to heptasaccharides, based on the total weight of FOS.

Oligofructose is commercially available, for example as RAFTILOSE@ from ORAFTI, (Tienen, Belgium), in various grades such as, for example, RAFTILOSE@ P95 which contains about 95 % by weight oligofructose, composed of chains with a degree of polymerisation ranging from 2 to about 7, typically with a (DP) of 3.5 to 4.5, and containing about 5 % by weight in total of glucose, fructose and sucrose.

Galacto-oligosaccharides (GOS) may comprise di, tri, tetra, penta and hexasaccharides, mainly consisting of galactose as a sugar component, and are formed by the action of beta-galactosidase on lactose. According to the invention, GOS may comprise between 2 and 15 saccharide units, preferably between 2 to 10 saccharide units, more preferably between 2 to

7 saccharide units and even more preferably between 2 to 6 saccharide units. In one embodiment of the invention, GOS may contain about 0 to about 45% of weight disaccharides, preferably about 10 to about 40% of weight disaccharides, more preferably about 20 to about 35% of weight disaccharides, and even more preferably about 33% of weight disaccharides, based of the total weight of GOS. According to the invention, GOS may contain about 0 to about 50% of weight trisaccharides, preferably about 10 to about 45% of weight trisaccharides, more preferably about 20 to about 40% of weight trisaccharides, and even more preferably about 39% of weight trisaccharides, based of the total weight of GOS. According to the invention, GOS may contain about 0 to about 50% of weight tetrasaccharides, preferably about 5 to about 45% of weight tetrasaccharides, more preferably about 10 to about 40% of weight tetrasaccharides, and even more preferably about 18% of weight tetrasaccharides, based of the total weight of GOS. According to the invention, GOS may contain about 0 to about 30% of weight pentasaccharides, preferably about 1 to about 25% of weight pentasaccharides, more preferably about 2 to about 10% of weight pentasaccharides, and even more preferably about 7% of weight pentasaccharides, based of the total weight of GOS.

As used throughout the specification and claims, the term "soluble fiber" refers to fibers which are able to undergo fermentation in the colon to produce short chain fatty acids (SCFA). Examples of soluble fibres are: pectin, guar gum, e.g. hydrolyzed guar gum, e.g. partially hydrolyzed guar gum, and gum arabic.
The hydrolysed soluble fiber may be derived from numerous known soluble fibers, including from locust bean gum, xanthan gum, guar gum, and pectin. The preferred fibers, for numerous reasons set forth below are hydrolysed guar gum, e.g. partially hydrolyzed guar gum and hydrolysed pectin; hydrolysed guar gum and partially hydrolyzed guar gum being the most preferred. The term hydrolysed soluble fibers as used herein refers to soluble fibers hydrolysed in conventional manner, e.g. chemically or enzymatically to soluble fibers having a reduced molecular weight, which hydrolysed products are tube compatible when administered at the desired daily amount.

A particularly preferred hydrolysed guar gum is Benefiber®, e.g. as described in U.S. Patent No. B1 5,260,279, which is hereby incorporated by reference. Prior to hydrolysis, the molecular weight of guar gum is approximately 200,000; after hydrolysis it is 20,000-30,000.

For use in accordance with this invention, the molecular weight range of the hydrolysed guar gum may vary, preferably may be between 24 and 30 kDa.

The relative proportion of the active ingredients of the compositions of the invention will, of course, vary considerably depending on the particular type of composition concerned, e.g. whether it is a liquid or solid form, or whether it is provided in nutritional form. All indicated proportions and relative weight ranges described herein are accordingly to be understood as being indicative of preferred or individually inventive teaching only and not limiting the invention in its broadest aspect.

As used herein, the term cis-polyunsaturated fatty acid refers to a family of carboxylic acids comprising n-3 fatty acids such as alpha-linolenic acid (18:3), stearidonic acid, eicosapentaenoic acid (EPA) (20:5), docosapentaenoic acid (22:5) and docosahexaenoic acid (DHA) (22:6), and n-6 fatty acids such as linoleic acid (18:2), gamma-linolenic acid (18:3), arachidonic acid (20:4), either in free form or in form of an oil or fat. Such cis-polyunsaturated fatty acids are commonly known and readily commercially available. They are present for example in vegetable oils or fish oils.
Preferably a combination of eicosapentaenoic acid and docosahexaenoic acid may be used.

In one embodiment of the invention, compositions of the invention may also comprise fibers and proteins. Fibers in particular include soluble and insoluble non-digestible polysaccharides, such as non-starch polysaccharides, e.g. of cellulose, hemicellulose, resistant starch, gums, etc.

Further components of the compositions according to the invention may include any bioactive compounds or extracts which are known to have health benefits, especially compounds which have a beneficial influence on the gastro-intestinal tract, such as glutamine/glutamate or precursors thereof. The compositions of the invention may also contain one or more additional substances that inhibit bacterial adhesion to epithelial wall of the gastrointestinal tract, including mannans, galacturonic acid oligomers, preferably of natural origin. The composition of the invention may be combined with drugs usefull for the treatment of ulcerative colitis, such as sulphasalazine, 5-ASA agents, corticosteroids, such as adrenal steroids, prednisone, hydrocortisone or budesonide; or drugs used against pain,

diarrhea, infection or IBS, such as a serotonin-4 receptor agonist, e.g. Zelnorm/Zelmac™. For example, the composition of the invention may be provided in the form of a kit for separate, sequential or simultaneous administration in conjunction with such medicines as described herein above. These medicines may conveniently be formulated together with the composition of the invention in standard pharmaceutical dosage forms.

In one aspect of the present invention, the compositions according to the invention can readily be incorporated into pharmaceutical or nutritional formulations, typically nutraceuticals, dietary supplements, functional food and beverage products.

In a further aspect of the invention, the compositions of the invention may be used as a medicament. Accordingly the compositions of the invention may be administered in pharmaceutical form or as a dietary supplement, preferably in combination with at least one pharmaceutically or nutritionally acceptable carrier.

In a yet further aspect of the invention, there is provided a medicament, nutritional or pharmaceutical formulation, for example dietary supplement, comprising the composition of the invention. The medicament, nutritional or pharmaceutical composition of the invention may optionally comprise pharmaceutical acceptable carriers. Further, according to the invention there is provided a combined pharmaceutical preparation for simultaneous, separate or sequential use for maintaining and/or restoring the gut microflora or for eliminating Sulfate reducing bacteria, for the treatment or prevention of IBD, in particular Ulcerative Colitis , Crohn's disease, and/or colon cancer, for repressing or prolonging the remission periods on Ulcerative patients,and/or for the prevention or treatment of IBS or its syndromes.

Pharmaceutical compositions and dietary supplements may be provided in the form of soft gel, sachets, powders, syrups, liquid suspensions, emulsions and solutions in convenient dosage forms. In soft capsules the active ingredients are preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols. Optionally stabilisers may be added.

Oral pharmaceutical or dietary supplement forms may be made by conventional compounding procedures known in the pharmaceutical art, that is, by mixing the active

substances together with edible pharmaceutically acceptable solid or liquid carriers and/or excipients, e.g. fillers such as cellulose, lactose, sucrose, mannitol, sorbitol, and calcium phosphates and binders, such as starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone (PVP). Optional additives include lubricants and flow conditioners, e.g. silicic acid, silicon dioxide, talc, stearic acid, magnesium/calcium stearates, polyethylene glycol (PEG) diluents, disintegrating agents, e.g. starch, carboxymethyl starch, cross-linked PVP, agar, alginic acid and alginates, colouring agents, flavouring agents, and melting agents. Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Optionally, the compositions according to the invention may be nutritionally complete, i.e. may include vitamins, minerals, trace elements as well as nitrogen, carbohydrate and fatty acid sources so that they may be used as the sole source of nutrition supplying essentially all the required daily amounts of vitamins, minerals, carbohydrates, fatty acids, proteins and the like. Accordingly, the compositions of the invention may be provided in the form of a nutritionally balanced complete meal, e.g. suited for oral or tube feeding.

Alternatively, the compositions of the invention may be provided as part of a meal, i.e. a nutritional supplement, e.g. in the form of a health drink.

It may be desirable to provide the composition of the invention in the form of a low calorie meal replacement or other nutritional product. In this case the meal replacement or other nutritional product is preferably low fat, i.e. less than about 10 en%, or substantially fat-free, i.e. less than about 2.5 en% contributed by fat, such as about 2 en% fat, based on the total caloric content of the composition. Suitably, a single serving of a low calorie meal replacement will have a caloric value of less than about 1000kcal, and preferably between about 200kcal and about 500kcal. Suitable low calorie nutritional product may include soft drink, such as juice, smoothie or soy-based drink, or dispersed in foods of any sort, such as, dairy bars, soups, breakfast cereals, müesli, candies, tabs, cookies, biscuits, crackers, such as a rice crackers, and dairy products, such as milk-shake, yoghurt drink.

The compositions of the invention optionally comprise conventional food additives, such as any of emulsifiers, stabilizers, sweeteners, flavourings, colouring agents, preservatives,

chelating agents, osmotic agents, buffers or agents for pH adjustment, acidulants, thickeners, texturisers, and so on.

In a further aspect of the invention, there is provided a use of compositions of the invention as food additive.

Suitable product formats according to the present invention include solution, ready-for-consumption composition, e.g. ready-to-drink compositions, instant drink, liquid comestibles, like soft drinks, juice, sports drinks, milk drinks, milk-shakes, yogurt drinks or soup. In a further embodiment of the invention, the compositions of the present invention may be manufactured and sold in the form of a concentrate, a powder, or granules, e.g. effervescent granules, which are diluted with water or other liquid, such as milk or fruit juice, to yield a ready-for-consumption composition, e.g. ready-to-drink compositions or instant drink.

The compsition of the invention may be in any form suitable for human administration, and in particular for administration in any part of the gastrointestinal tract. Enteral administration of the compositions of the invention, and preferably oral administration, and administration through a tube or catheter, are covered by the present invention.

The amount and dosage regimen of the compositions of the invention to be administered is determined in the light of various relevant factors including the purpose of administration, the age, sex and body weight of individual subject and the severity of the subject's symptoms.

The compositions of the invention may be administered under the supervision of a medical specialist, or may be self-administered.

Pharmaceutical, food or beverage incorporating compositions according to the invention can be safely-consumed by anyone, and are especially recommended for anyone perceived to be at risk from diseases, conditions and symptoms related to IBD, in particular Ulcerative Colitis , Crohn's disease, colon cancer or IBS as hereinabove described.

In one embodiment of the invention, the invention pertains to a method of treating and/or preventing diseases, conditions and symptoms related to IBD, in particular Ulcerative Colitis , Crohn's disease, colon cancer or IBS as hereinabove described, in a mammal, including

human, in need of such a treatment, comprising administering to said mammal an effective amount of a composition according to the invention. As used herein, the term "an effective amount" refers to an amount effective to achieve a desired therapeutic effect, such as treating and/or preventing diseases, conditions and symptoms related to IBD, in particular Ulcerative Colitis, Crohn's disease, colon cancer or IBS as hereinabove described.

In another embodiment of the invention, the compositions according to the invention may be used in the manufacture of a medicament or nutritional formulation for the prevention or treatment of diseases, conditions and symptoms related to IBD, in particular Ulcerative Colitis , Crohn's disease, colon cancer or IBS as hereinabove described in mammal, including human.

In another embodiment, the present invention relates to a process for the production of the production of the invention, wherein such a process comprises intimately admixing the components of the composition of the invention. Such processes are well known to one skilled in the art.

Examples

The Fructooligosaccharides (FOS), used as positive control, is Actilight 950P®, Beghin-Meiji industries, France (containing 92% oligosaccharides),

The Galactooligosaccharides (GOS) is Elixor®, Borculo Domo Ingredients, Netherlands (containing 58% oligosaccharides, 23% lactose, 19% glucose).

The Xylooligosaccharides (XOS) is Xylo-oligo 95P®, Suntory Limited, Japan (containing 91% oligosaccharides).

The Soyaoligosaccharides (SOS) is Soybean Oligosaccharides Syrup, Soya Oligo Japan Inc., Japan (containing 23% oligosaccharides, 21% sucrose, 31% other saccharides).
The Arabinogalactan (ABG) is ClearTrac AG-99®, Larex Inc., USA (containing 95% soluble fibers).

The Acacia gum (AG), also called gummi arabicum, is Fibregum®, Colloides Naturels International, France (containing 85% soluble fibers).

The Wheat germ (WG) is Biogerm PB1®, Multiforsa, Switzerland (containing 32% oligosaccharides, 30% protein, 12% fibers, 7% fat).

The Isomaltooligosaccharides (IMO) is Isomalto 900®, Showa Sangyo Co., Japan (containing 89% oligosaccharides).

Example 1: *in vitro* study of the prebiotic potential of several oligosaccharides and mixture thereof.

1. Method

The prebiotic potential of fructooligosaccharides (FOS), galactooligosaccharides (GOS), xylooligosaccharides (XOS), soyaoligosaccharides (SOS), arabinogalactan (ABG), acacia gum (AG), wheat germ (WG) and isomaltooligosaccharides (IMO) was determined using *in vitro* faecal batch cultures. Similarly, the prebiotic potential of mixtures of oligosaccharides, namely, FOS + GOS, AG + FOS, FOS+XOS, XOS +GOS and AG + GOS, in equal ratios was investigated *in vitro*. FOS was used as a positive control, against which the prebiotic nature of the test carbohydrates was compared. Faecal batch cultures using the test compound(s) as sole carbohydrate sources were conducted using faecal inocula from 6 healthy adults to ensure both biological and statistical relevance. A prebiotic index was constructed in order to rank the prebiotic capabilities of the test compounds.

Faecal samples cultures using the test compound(s) as sole carbohydrate sources were conducted using faecal inocula from 6 healthy human volunteers who were free of known metabolic and gastrointestinal diseases (e.g. diabetes, ulcerative colitis, Crohn's disease, peptic ulcers and cancer). The samples were collected on site, kept in the anaerobic cabinet and used within a maximum of 5 minutes after collection. A 1:10 dilution in 0.1M anaerobic phosphate buffer (pH 7.4) was prepared and the samples homogenised in a stomacher for 2 minutes.

(a) *Batch cultures*

90 ml sterile chemostat medium was maintained under anaerobic conditions (continuous gassing with O_2 free N_2), at 37°C in stirred chemostat vessels. The culture pH was maintained at 6.7. The carbohydrate sources, 10 % weight /volume, were then added. Each vessel was inoculated with a 10 ml fresh human faecal suspension (10 % w/v) prepared in anaerobic phosphate buffered saline. Batch cultures were maintained for 24 hours.

(b) *Bacterial Enumeration*

Samples of the batch culture were taken at 0, 5, 10 and 24 hours of growth. Fluorescent *in situ* hybridisation was used for the bacteriology, with total bacteria, *Bacteroides* spp., *Bifidobacterium* spp., *Clostridium perfringens/histolyticum* subgroup and the *Lactobacilli* being enumerated using group specific fluorescentally labelled DNA probes targeting 16S rRNA.

(c) *Prebiotic Index*

The prebiotic ranking takes into account the positive effect of bifidobacteria and lactobacilli and the negative effect of clostridia and bacteroides. It is expressed as the sum of changes in numbers of bifidobacteria and lactobacilli between 0 h and 10 h or 24 h, minus the sum of changes in numbers of bacteroides and clostridia over the same period.

Prebiotic Index at 24 hours of fermentation = $((Bif_{24} - Bif_0) + (Lac_{24} - Lac_0)) - ((Bac_{24} - Bac_0) + (Clos_{24} - Clos_0))$
[cells/ ml batch culture]

2. Results

The results presented and discussed here are the combined results for 6 runs of each different potential prebiotic.

FOS + GOS was selectively and highly fermented by bifidobacteria after both 10 and 24 hours of fermentation. The increase was at both points higher than during the fermentation of FOS or GOS alone. Bacteroides numbers decreased slightly. The combination exhibited one of the largest increases of all test substrates in lactobacilli during the first 10 hours of

fermentation. The increase was not maintained after 24 hours, but numbers stayed above initial levels. Although clostridia showed a small increase at 10 hours, numbers dropped after 24 hours below initial levels. A very small decrease in bacteroides numbers was observed after 24 h. FOS+GOS was utilised quickly by bifidobacteria and lactobacilli and increased numbers much higher than FOS or GOS alone. This relatively large increase in lactobacilli after 10 hours of fermentation is very important as prebiotics are usually fermented by bifidobacteria causing little if any change in lactobacilli. It seems that the combination synergistically increases numbers of the beneficial bacteria.

3. Discussion

Results showed clearly that oligosaccharides are fermented much more selectively by the beneficial bacteria, mainly bifidobacteria and lactobacilli than the soluble fibers tested in this trial.

The combination **FOS and GOS** acts synergistically, and enhances surprisingly bifidobacteria and lactobacilli to much higher amounts than when these oligosaccharides were tested alone. The less beneficial bacteria seem not be influenced by the combination towards a reduction in numbers, but rather increased slightly, as compared to both oligosaccharides tested separately.

The prebiotic index considers the effect on growth of the beneficial and the less desired bacteria species. Therefore an ingredient, which increases numbers in bifidobacteria and lactobacilli and which also are able to decrease numbers of the less beneficial, such as clostridia and bacteroides have high prebiotic ranking. They are especially good prebiotics due to their property to enhance growth selectively. The combination of FOS and GOS showed clearly of all ingredients and combination tested the best prebiotic ranking over the entire fermentation period.

Example 2: nutritional composition: for 100 g

FOS	1g
GOS	1g

Benefiber	0.2g
Glutamine	1g
EPA	0.43g
DHA	0.28g

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Claims

1. A nutritional or pharmaceutical composition comprising FOS and GOS.

2. A composition according to claim 1 wherein said composition comprises polyunsaturated fatty acids chosen from at least one of alpha-linolenic acid (18:3), stearidonic acid, eicosapentaenoic acid (EPA) (20:5), docosapentaenoic acid (22:5) and docosahexaenoic acid (DHA).

3. A composition according to claim 1 or 2 for use as a medicament.

4. Use of a composition according to claim 1 or 2 in the manufacture of a medicament or nutritional composition for maintaining and/or restoring the intestinal flora, for improving the gut microflora or for eliminate sulphide reducing bacteria.

5. Use of a composition according to claim 1 or 2 in the manufacture of a medicament or nutritional composition for the prevention or treatment of inflammatory bowel disease, in particular ulcerative colitis, Crohn's disease, and/or to prevent colon cancer.

6 Use of a composition according to claim 1 or 2 in the manufacture of a medicament or nutritional composition for repressing or prolonging the remission periods on Ulcerative Colitis patients.

7 Use of a composition according to claim 1 or 2 in the manufacture of a medicament or nutritional composition for the prevention or treatment of Irritable Bowel Syndrome or its syndromes.

8 A method of maintaining and/or restoring the intestinal flora in a mammal in need of such a treatment comprising administering to said mammal an effective amount of a composition according to any one of claim1 or 2.

9 A method of treating and/or preventing inflammatory bowel disease, ulcerative colitis, Crohn's disease and/or to prevent colon cancer in a mammal in need of such a treatment

comprising administering to said mammal an effective amount of a composition according to claim 1 or 2.